

TOWNSEND
and
TOWNSEND
and
CREW
LLP

OFFICIAL

San Francisco, California
Tel 415 576-0200

Palo Alto, California
Tel 650 326-2400

San Diego, California
Tel 858 350-6100

Denver, Colorado
Tel 303 571-4000

Seattle, Washington
Tel 206 467-9600

Walnut Creek
2175 North California Blvd.
Suite 625
Walnut Creek
California 94596
Tel 925 472-5000
Fax 925 472-8895

FACSIMILE COVER SHEET

Date: October 06, 2003	Client & Matter Number: 015390-000130	No. Pages (including this one): 46
To: Examiner Christina Chan PTO	At Fax Number: 703-746-5030	Confirmation Phone Number: 703-308-3973
From: Eugenia Garrett-Wackowski (3005)		

Message:

Re: Application No. 08/973,576 - Bernard Malfry-Camine - Filed: December 5, 1997

Pursuant to your recent request, attached are the original and two copies of the revised Appeal Brief for the above-identified application.

Original Will:	<input type="checkbox"/>	BE SENT BY MAIL	<input type="checkbox"/>	BE SENT BY FEDEX/OVERNIGHT COURIER	<input type="checkbox"/>	BE SENT BY MESSENGER	<input checked="" type="checkbox"/>	NOT BE SENT
----------------	--------------------------	-----------------	--------------------------	------------------------------------	--------------------------	----------------------	-------------------------------------	-------------

Faxed: Return to: Linda L. Shaffer - (3007)

If you have problems with reception please call Fax Services at extension

Important

This message is intended only for the use of the individual or entity to which it is addressed and may contain information that is privileged, confidential, and/or exempt from disclosure by applicable law or court order. If the reader of this message is not the intended recipient, or the employee or agent responsible for delivering the message to the intended recipient, you are hereby notified that any dissemination, distribution, or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by telephone and return the original message to us at the above address via the United States Postal Service. Thank you.

60054013 v1

PATENT

Attorney Docket No. 15390-000130

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of:

Bernard Malfroy-Camine

Application No.: 08/973,576

Filed: December 5, 1997

For: TRANSVASCULAR AND
INTRACELLULAR DELIVERY OF
LIPIDIZED PROTEINS

Examiner: R. Schwadron

Art Unit: 1644

APPELLANT'S BRIEF UNDER 37 CFR
§1.192Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The following is Appellant's Appeal Brief submitted in triplicate pursuant to 37
C.F.R. § 1.192(a).

TABLE OF CONTENTS

	Page i
REAL PARTY IN INTEREST:.....	1
RELATED APPEALS AND INTERFERENCES:.....	1
STATUS OF CLAIMS:	1
STATUS OF RECENT AMENDMENTS:.....	1
SUMMARY OF THE INVENTION:.....	2
ISSUES:	2
GROUPING OF THE CLAIMS:	3
ARGUMENTS.....	3
a. <i>The Rejection Under 35 U.S.C. § 112, First Paragraph</i>	<i>3</i>
b. <i>The Teachings of the Specification Provide More Than Sufficient Guidance to One of Skill in the Art to Make and Use the Claimed Invention.....</i>	<i>4</i>
c. <i>Horan et al. Does Not Support the Unpredictability of Intracellular Localization of Lipidized Proteins with Hydrocarbon Tails of Greater than 12 Carbons.....</i>	<i>5</i>
d. <i>35 U.S.C. §112, First Paragraph, Does Not Require that Appellant Predicts, A Priori, Which Lipidized Proteins Will Localize Intracellularly</i>	<i>7</i>
CONCLUSION	9

Bernard Malfroy-Camine
Application No.: 08/973,576
Page 1

REAL PARTY IN INTEREST:

Eukarion, Inc. is the assignee of the above-referenced patent application and, thus, the real party in interest.

RELATED APPEALS AND INTERFERENCES:

Appellant's legal representative and the assignee of the above-referenced patent application have filed an appeal in related Application No. 08/483,944, wherein similar claims and rejections are present.

STATUS OF CLAIMS:

Claims 1-23 were originally filed in the above-referenced patent application. Claims 23 was cancelled by amendment mailed on April 27, 1999. New claim 24 (it is noted that there was a typographical error in the amendment, which stated new claim 23, instead of new claim 24) was added by amendment faxed on February 29, 2000. Claims 1-22 and 24 stand finally rejected and are being appealed. All of the claims being appealed are set forth in Appendix A for the convenience of the Board of Appeals.

STATUS OF RECENT AMENDMENTS:

Appellant filed an Amendment on April 27, 1999 in response to the Office Action mailed October 27, 1999. In response to the Amendment, Appellant received a final Office Action mailed July 15, 1999. Appellant filed an Amendment After Final on January 14, 2000 and a Supplemental Amendment After Final on February 29, 2000. In response to the Amendment After Final and the Supplemental Amendment After Final, Appellant received an Office Action mailed May 24, 2000. Appellant filed an Amendment on August 23, 2000. In response to the Amendment, Appellant received a final Office Action mailed November 6, 2000. In response to the final Office Action, Appellant filed a Notice of Appeal on May 7, 2001. Appellant then filed a Request for Continued Prosecution, a Request for Reconsideration and a Declaration of Dr. Bernard Malfroy-Camine pursuant to 37 C.F.R. § 1.132 on December 7, 2001. In response to the Request for Continued Prosecution, Appellant received a final Office Action mailed March 21, 2002. Appellant filed a Request For Reconsideration and a second Declaration of Dr. Bernard Malfroy-Camine pursuant to 37 C.F.R. § 1.132 on August 21, 2002 and a Notice

!
Bernard Malfroy-Camine
Application No.: 08/973,576
Page 2

of Appeal on September 20, 2002. Appellant received an Advisory Action mailed September 25, 2002. All Amendments have been entered.

SUMMARY OF THE INVENTION:

The present invention relates generally to methods for targeting proteins, such as antibodies, to intracellular compartments in a eukaryotic cell, to methods for enhancing organ uptake of proteins, to pharmaceutical compositions comprising lipidized proteins for use in human therapy, and to methods for making such lipidized proteins (*see, e.g.*, the specification at page 1, lines 8-16; and at page 45, lines 2-12; and claims 1-12 and 24-34, *etc.*).

More particularly, the present invention is directed to lipidized proteins, such as lipidized antibodies. It has surprisingly been found that the lipidized proteins of the present invention are capable of transvascular transport, organ uptake and intracellular localization (*see, e.g.*, the specification at page 5, lines 18-34; at page 5, line 35 through page 6, line 13; at page 7, line 31 through page 8, line 36; at page 15, lines 14-17; at page 18, line 38 through page 19, line 15; and at page 28, line 29 through page 29, line 16, *etc.*). As such, all of the pending claims are directed to a lipidized protein (*e.g.*, a lipidized antibody) that is a protein (*e.g.*, an antibody) covalently linked to a lipid through a carbohydrate moiety, and that is capable of transvascular transport, organ uptake and intracellular localization (*see, claims 1-22 and 24*). Moreover, the present invention is directed to methods of making such lipidized proteins and to compositions comprising such lipidized proteins (*see, e.g.*, the specification at page 5, lines 11-17 and 18-34; at page 6, lines 1-13; page 12, line 37 through page 9, line 2, at page 15, lines 17-37; at page 16, line 1 through page 18, line 37; Figure 2; and the examples at page 30, line 8 through page 40, line 8, *etc.*).

ISSUES:

1. Based on the teachings in the specification and in view of the general knowledge in the art, could one of ordinary skill in the art practice the claimed invention, as of the filing date of the above-referenced patent application, *without* "undue" experimentation?
2. Upon receiving an indication regarding allowable subject matter, will the filing of a Terminal Disclaimer and/or canceling the conflicting subject matter from copending U.S. Patent Application No. 08/973,576 overcome the obviousness-type double patenting rejection?

Bernard Malfroy-Camine
Application No.: 08/973,576
Page 3

GROUPING OF THE CLAIMS:

The Examiner has maintained the rejection of claims 1-22 and 24 under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. The Examiner has indicated that claims 6 and 11 are enabled by the specification as originally filed and, thus, would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. As such, with respect to the § 112, first paragraph, rejection, claims 1-5, 7-10, 12-22 and 24 stand together, and claims 6 and 11 stand on their own.

In addition, the Examiner has maintained the provisional rejection of claims 14-22 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4-12, 24 and 29-33 of copending U.S. Patent Application No. 08/483,944. As such, with respect to the obviousness-type double patenting rejection, claims 14-22 stand together, and claims 1-13 and 24 stand on their own.

ARGUMENTS

ISSUE 1: § 112, FIRST PARAGRAPH, REJECTION

a. *The Rejection Under 35 U.S.C. § 112, First Paragraph*

Claims 1-5, 7-10, 12-22 and 24 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the Examiner has stated that while the specification as filed is enabling for the use of glycyldioctadecylamide for lipidizing proteins in order to achieve intracellular localization of the lipidized protein, the specification allegedly does not enable the use of any other lipid having a hydrocarbon tail of greater than 12 carbons for making lipidized proteins that localize intracellularly. In support of this rejection, the Examiner cites Horan *et al.* (U.S. Patent No. 5,665,328), and states that it is unpredictable whether lipidized proteins that contain a hydrocarbon tail of more than 12 carbons will localize intracellularly.

Bernard Malfroy-Camine
Application No.: 08/973,576
Page 4

Appellant respectfully traverses this rejection. A particular claim is enabled by the disclosure in an application if the disclosure, at the time of filing, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention without undue experimentation. *See, e.g., In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988), or MPEP § 2164.01. In addition, "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." *See*, MPEP § 2164.01. For the reasons set forth herein, Appellant respectfully submits that undue experimentation would *not* be required to use a lipid having a hydrocarbon tail of greater than 12 carbons for making lipidized proteins that localize intracellularly.

b. The Teachings of the Specification Provide More Than Sufficient Guidance to One of Skill in the Art to Make and Use the Claimed Invention

As previously explained, the present claims are directed to lipidized proteins, such as lipidized antibodies, that localize intracellularly. Therefore, to make and use the claimed invention, one of skill would have simply needed to obtain proteins (e.g., antibodies), obtain lipids, attach the lipids to the proteins (e.g., antibodies), and determine whether the resulting lipidized protein localized intracellularly. Appellant points out that each of these requirements is amply taught in the specification as originally filed. For example, the specification at page 12, lines 18-37; page 13, lines 1-11; page 19, lines 34-37; page 20, lines 1-37; and page 21, line 1-12, *inter alia*, teaches suitable proteins/antibodies and their preparation. Moreover, the specification at page 17, lines 20-37; page 18, lines 1-40; page 19, lines 1-2, *inter alia*, teaches suitable lipids, such as lipoamines, lipopolyamines, and fatty acids, for use in the compositions and methods of the present invention. In addition, the specification at page 15, lines 30-37; page 16, lines 1-32; page 33, lines 6-37; and page 34, lines 1-2, *inter alia*, teaches methods for attaching a lipid to a protein by a covalent linkage to a carbohydrate side chain of the protein. By way of illustration, lipoamines having varying lengths of hydrocarbon chains are described at pages 17-18 of the specification. Methods for attaching these various lipid substituents to proteins are described at, *e.g.*, page 18, lines 30-32, and in Example 1 of the specification.

Importantly, the present specification also teaches a variety of methods for testing or screening whether a given lipidized protein localizes intracellularly (*see, for example*, page

Bernard Malfroy-Camine
Application No.: 08/973,576
Page 5

34, lines 17-36; page 35, lines 1-8; page 35, lines 13-37; and page 36, lines 1-23). For example, as described in the specification, lipidized proteins can be radiolabeled, and their uptake by organs can be evaluated (see, e.g., page 31 of the specification). In another example, a lipid substituent can be attached to an anti-Tat antibody, and its ability to protect cells from HIV-1 virus infection can be evaluated (see, e.g., pages 32 and 33 of the specification). Moreover, standard techniques were available at the time the application was filed for determining the cellular localization of a protein, i.e., whether a protein is localized inside the cell or at the cell membrane.

In view of the foregoing, Appellant respectfully submits that the specification thus discloses how to make lipidized proteins, and how to appropriately determine whether the lipidized protein localizes intracellularly. As such, one of skill in the art would have been able to make and practice the present invention *without* "undue" experimentation.

c. *Horan et al. Does Not Support the Unpredictability of Intracellular Localization of Lipidized Proteins with Hydrocarbon Tails of Greater than 12 Carbons*

As explained above, the Examiner cites Horan *et al.* (U.S. Patent No. 5,665,328) as supporting the position that it is unpredictable whether lipidized proteins that contain a hydrocarbon tail of more than 12 carbons will localize intracellularly.

Appellant respectfully *disagrees* and, in doing so, submits that Horan *et al.* does *not* support the unpredictability of intracellular localization of lipidized proteins with hydrocarbon tails of greater than 12 carbons. In support of this position, Appellant refers the Examiner once again to the declaration of Dr. Bernard Malfroy-Camine, which was filed in the present case on August 21, 2002 pursuant to 37 C.F.R. § 1.132.

As stated by Dr. Malfroy-Camine in his declaration, it may be helpful to clarify the description in Horan *et al.* relied upon by the Examiner. Horan *et al.* generally describes bio-affecting compounds having a hydrocarbon substituent for binding to the cell membrane surface (see, e.g., col. 3, lines 25-42). By contrast, the present invention is directed to lipidized proteins, i.e., proteins that are covalently linked to a lipid through a carbohydrate moiety, that are capable of transvascular transport, enhanced organ uptake and *intracellular localization*. Thus, the problem being solved by Horan *et al.* differs completely from that of the present invention.

Bernard Malfroy-Camine
Application No.: 08/973,576
Page 6

Moreover, as stated by Dr. Malfroy-Camine in his declaration, Horan *et al.* does *not* stand for the proposition that it is unpredictable whether lipidized proteins that contain a hydrocarbon tail of greater than 12 carbons will localize intracellularly. Rather, Horan *et al.* was concerned with determining a suitable hydrocarbon tail length for binding a bio-affecting compound with the hydrocarbon tail *to the cell membrane surface*. For example, Horan *et al.* describe that the number of linear carbons in the hydrocarbon tails of the compounds together with the chemical nature of the bio-affecting moiety are important factors in achieving binding of the compounds to the cell membrane surface (*see, col. 3, lines 52-56*). Horan *et al.* further states the following:

Experience with use of cyanine derivatives as diagnostic agents indicates that hydrocarbon tails of less than 3 carbons causes the cyanine to penetrate the plasma membrane and the nuclear membrane of cells resulting in staining of RNA and DNA. If carbon tails have a length greater than 3 carbons and less than 12 carbons, the compound no longer binds RNA and DNA but responds to membrane potential and enters the mitochondria... When the sum of the linear carbons in the hydrocarbon tail(s), is 23 or greater the lipophilicity of the molecule is increased such that it is retained in the plasma membrane and will not leak or transfer to other cells.... Thus, there may be a practical limitation on the length of the hydrocarbon tail(s) *depending on the chemical nature of the bio-affecting moiety to which it is to be bound*.

*See, col. 3, line 56 to col. 4, line 12, of Horan *et al.* (emphasis added).* As shown in the emphasized passage, the length of the hydrocarbon tails suitable for binding the bio-affecting compounds to cell membrane surface depends on the chemical nature of the bio-affecting moiety to which it is bound. Therefore, Horan *et al.* does *not* support the Examiner's statement that it is unpredictable whether any lipidized proteins that contain hydrocarbon tails of greater than 12 carbons will localize intracellularly.

In fact, the present specification provides working examples that a lipidized protein with a hydrocarbon tail of greater than 12 carbons, namely glycyldioctadecylamide, is capable of localizing intracellularly. For example, glycyldioctadecylamide was linked to bovine IgG (*see, Example 1 at pages 30-31 of the specification*). This lipidized protein was labeled with ¹⁴C, and was administered intravenously to mice. It was shown that the lipidized

Bernard Malfroy-Camine
Application No.: 08/973,576
Page 7

proteins were taken up by various organs, such as brain, liver, spleen and kidney. In another example, a monoclonal antibody that specifically binds to Tat protein of HIV-1 was lipidized with glycidioctadecylamide (see, Example 2 at page 32-33 of the specification). It was shown that when cells were pretreated with the lipidized anti-Tat antibody prior to addition of HIV-1 virus, the treated cells were almost completely protected from the cytopathic effects of the HIV-1 virus. By contrast, cells that were treated with native anti-Tat antibody or that were untreated were not protected from the cytotoxic effect of the HIV-1 virus. These results *unequivocally* establish that lipidized proteins with a hydrocarbon tail of greater than 12 carbons can, in fact, localize intracellularly.

d. 35 U.S.C. §112, First Paragraph, Does Not Require that Appellant Predicts, A Priori, Which Lipidized Proteins Will Localize Intracellularly

Finally, the Examiner is reminded that the Appellant is not required to predict, *a priori*, which lipidized proteins will localize intracellularly or not. The key issue under 35 U.S.C. §112, first paragraph, is whether or not "undue" experimentation is required to make or use the claimed invention. As explained by the Court of Customs and Patent Appeals in *In re Angstadt*, 190 U.S.P.Q. 214, 219 (CCPA 1976):

[i]f the disclosure must provide "guidance which will enable one skilled in the art to determine, *with reasonable certainty before performing the reaction*, whether the claimed product will be obtained" (emphasis in original), as the dissent claims, then all "experimentation" is "undue," since the term "experimentation" implies that the success of the particular activity is *uncertain*. Such a proposition is contrary to the basic policy of the Patent Act, which is to encourage disclosure of inventions and thereby to promote progress in the useful arts.

Assuming *arguendo* that one would not have been able to predict whether certain lipidized proteins will localize intracellularly, the alleged lack of predictability does not render a claim invalid under 35 U.S.C. §112 unless "undue" experimentation is required to make the claimed products. As explained above and as explained by Dr. Malfroy-Camine in his declaration, *no* undue experimentation would be required to practice the invention as claimed. Again, the specification teaches how to make the claimed lipidized proteins and, importantly, the

Bernard Malfroy-Camine
Application No.: 08/973,576
Page 8

specification provides assays for testing, *i.e.*, screening, whether a given lipidized protein will localize intracellularly. Accordingly, the pending claims are, in fact, enabled by the specification as originally filed.

In conclusion, there is *no* compelling objective basis to believe that lipidized proteins with a lipid substituent other than glycyldioctadecylamide will not localize intracellularly. Given the working examples and ample guidance provided in the specification, one of skill in the art would have been able to make and use numerous other lipidized proteins having hydrocarbon tails of at least 12 carbons *without* undue experimentation. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph, is improper and withdrawal of the rejection is respectfully requested.

ISSUE 2: OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

In the Advisory Action mailed September 25, 2002, the Examiner has maintained the provisional rejection of claims 14-22 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4-12, 24 and 29-33 of copending U.S. Patent Application No. 08/483,944. In this same Advisory Action, the Examiner has acknowledged Appellant's indication that this issue will be addressed at a later date (*see*, page 2 of the Advisory Action). As explained in the Amendment filed August 21, 2020, upon receiving an indication regarding allowable subject matter, Applicant will cancel the conflicting claims in copending U.S. Patent Application No. 08/483,944 or, alternatively, file a Terminal Disclaimer. It is Appellant's understanding that filing a Terminal Disclaimer and/or canceling the conflicting claims, upon receiving an indication regarding allowable subject matter, should be more than sufficient to overcome this rejection.

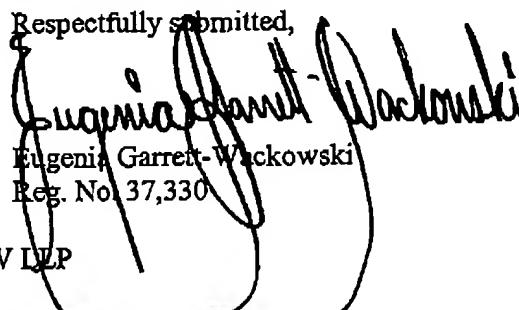
Bernard Malfroy-Camine
Application No.: 08/973,576
Page 9

CONCLUSION

In view of the foregoing remarks, Appellant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,


Eugenia Garrett-Wackowski
Reg. No. 37,330

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
(415) 576-0200
Fax (415) 576-0300
EGW/lis

Bernard Malfroy-Camine
Application No.: 08/973,576
Page 10

APPENDIX A

1. A method for making a lipidized protein, comprising the steps of:
attaching a lipid substituent having a hydrocarbon tail of at least 12 carbons to the protein by a covalent linkage of at least one lipoamine residue to a carbohydrate side chain to produce a lipidized protein; and
recovering the lipidized protein;

wherein:

the lipidized protein is capable of transvascular transport, enhanced organ uptake and intracellular localization.

2. A method according to claim 1, wherein the lipid substituent is a lipoamine.
3. A method according to claim 2, wherein the step of attaching further comprises the steps of
oxidizing a carbohydrate on a glycosylated polypeptide to produce an oxidized glycoprotein; and
reacting the oxidized glycoprotein with a lipoamine under suitable reaction conditions to form a lipidized protein.

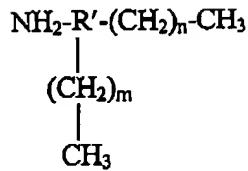
4. A method according to claim 2, wherein the lipoamine is a straight-chain lipoamine according to the formula:



where R is selected from the group consisting of: disubstituted alkyl (alkylene); 1,4-disubstituted cyclohexyl; disubstituted aryl (arylene); amido group of the formula $-(\text{CHR}_1)\text{-CO-NH-}$ wherein R₁ is hydrogen or an amino group; alkylcarbonyl; and phosphate diester; n is 10-50.

5. A method according to claim 2, wherein the lipoamine is a branched-chain lipoamine according to the formula:

Bernard Malfroy-Camine
Application No.: 08/973,576
Page 11



where R' is: a trisubstituted alkyl; a trisubstituted aryl; an amido group of the formula -(CHR₁)-CO-N< wherein R₁ is hydrogen or an amino group; an imido group of the formula -(CHR₂)-NH-CH< wherein R₂ is hydrogen or an amino group or an imido group of the formula -CH₂-N<; or a phosphate diester; m is 1-50; n is 10-50; and m and n are selected independently.

6. A method according to claim 5, wherein the branched-chain lipoamine is glycyldioctadecylamide.

7. A method according to claim 1, wherein the protein is a naturally-occurring glycoprotein.

8. A method according to claim 1, wherein the protein is encoded by an immunoglobulin superfamily gene.

9. A method for targeting an intracellular protein for binding with an antibody in a cell, comprising contacting the cell with a lipidized antibody which binds specifically with the intracellular protein, wherein said lipidized antibody is an antibody covalently linked to a lipid having a hydrocarbon tail of at least 12 carbons through a carbohydrate moiety and wherein said lipidized antibody is capable of transvascular transport, enhanced organ uptake and intracellular localization.

10. A method according to claim 7, wherein the lipidized antibody comprises at least one lipoamine residue linked to a carbohydrate side chain of an immunoglobulin.

11. A method according to claim 10, wherein the lipoamine is glycyldioctadecylamide.

Bernard Malfroy-Canine
Application No.: 08/973,576
Page 12

12. A method according to claim 9, wherein the lipidized antibody is administered to living mammalian cells *in vivo*.

13. A method according to claim 12, wherein the lipidized antibody is taken up into the living cells to a greater extent than a comparable antibody having the same amino acid sequence(s) and the same glycosylation pattern and lacking lipidation.

14. A composition comprising a therapeutically effective dosage of a lipidized protein and a pharmaceutically acceptable carrier, wherein said lipidized protein is a protein covalently linked to a lipid having a hydrocarbon tail of at least 12 carbons through a carbohydrate moiety and wherein said lipidized protein is capable of transvascular transport, enhanced organ uptake and intracellular localization.

15. A composition according to claim 14, wherein the lipidized protein is an antibody.

16. A composition according to claim 15, wherein the antibody binds to an intracellular protein.

17. A composition according to claim 16, wherein the intracellular protein is a viral-encoded protein.

18. A composition according to claim 17, wherein the viral-encoded protein is a Tat protein encoded by HIV-1.

19. A composition comprising a lipidized antibody and a pharmaceutically acceptable carrier, wherein a lipid substituent having a hydrocarbon tail of at least 12 carbons is covalently linked to the antibody by a covalent linkage of at least one lipoamine residue to a carbohydrate side chain to produce said lipidized antibody and wherein said lipidized antibody is capable of transvascular transport, enhanced organ uptake and intracellular localization.

20. A lipidized antibody, wherein said lipidized antibody is linked to a label selected from the group consisting of radionuclides, enzymes, enzymes substrates, enzyme

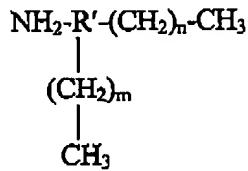
Bernard Malfroy-Camine
Application No.: 08/973,576
Page 13

inhibitors, ligands, radiocontrast agents and metal chelates, wherein a lipid substituent having a hydrocarbon tail of at least 12 carbons is covalently linked to the antibody by a covalent linkage of at least one lipoamine residue to a carbohydrate moiety to produce said lipidized antibody and wherein said lipidized antibody is capable of transvascular transport, enhanced organ uptake and intracellular localization.

21. The lipidized antibody of claim 20, wherein the antibody binds to an antigen intracellularly in living cells.

22. The lipidized antibody of claim 21, wherein the antibody binds to the HIV-1 Tat protein intracellularly in HIV-infected human cells.

24. A method according to claim 2, wherein the lipoamine is a branched-chain lipoamine according to the formula:



where R' is: a trisubstituted alkyl; a trisubstituted aryl; an amido group of the formula -(CHR₁)-CO-N< wherein R₁ is hydrogen or an amino group; an imino group of the formula -(CHR₂)-NH-CH< wherein R₂ is hydrogen or an amino group or an imino group of the formula -CH₂-N<; or a phosphate diester; m is 10-50; n is 1-50; and m and n are selected independently.

59060643 v1